Published in final edited form as:

Tetrahedron Lett. 2012 April ; 53(14): 1753–1755. doi:10.1016/j.tetlet.2012.01.101.

Deoxy Derivatives of L-like 5'-Noraristeromycin

Shante Hinton, Alecia Riddick, and Tesfaye Serbessa*

Elizabeth City State University, Department of Chemistry, Geology, and Physics, Elizabeth city, NC 27909

Abstract

Several base variations of 2'- and 3'-deoxy derivatives of (+)-4'-deoxy-5'-noraristeromycin have been prepared from enantiomerically pure precursors following standard purine nucleoside construction. These carbocyclic nucleosides were evaluated against hepatitis B virus (HBV) and found to be inactive. No cytotoxicity to the cell line was observed.

Keywords

L-like; carbanucleosides; HBV; Noraristeromycin

Introduction

Many years ago, the study of carbocyclic nucleosides lacking a methylene group at the 5'-position (5'-Norcarbanucleosides) was initiated.¹ Within this series of compounds, (+)-5'-noraristeromycin **1** (L-like) (Figure 1) was the first to show significant activity towards hepatitis B virus (HBV), while the (–)-enantiomer (D-like) was inactive.² Further investigation led to the discovery of (+)-4'-deoxy-5'-noraristeromycin **2**,³ which is ten times more potent in its activity against HBV. As part of an ongoing effort to determine the structural entities necessary for activity, base and cyclopentyl variations (compounds **3–8**) were designed and synthesized.

Chemistry

As depicted in scheme 1, target compounds **3–5** can be derived from S_N2 reaction of mesylate⁴ **9** (prepared from dicyclopentadiene in six steps) and a suitable base. For the preparation of **3**, the mesylate was added to a suspension of adenine **10** and sodium hydride in dimethylformamide (DMF). This resulted in the formation of the protected nucleoside **13**. The acetate group of **13** was then readily cleaved by using ammonia gas in anhydrous methanol to give **3**. A similar procedure was utilized to achieve the synthesis of **4** and **5**. A commercially available base, 2-amino-6-chloropurine **11**, was used for the synthesis of **4**. Compound **5**, however, required the preparation of the 7-deazapurine base **12** prepared from ethyl cyanoacetate and bromoacetaldehyde diethyl acetal in five steps⁵. Ammonolysis was employed to complete the synthesis of both target compounds.

© 2012 Elsevier Ltd. All rights reserved.

*Corresponding Author: telephone, (252)-335-3438; fax, 252-335-3508; tserbessa@mail.ecsu.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Optically active amino alcohol **16** was used in the synthesis of **6** (Scheme 2). The compound was prepared by utilizing enantioselective ring opening reaction of cyclopentene oxide (using trimethylsilyl azide) followed by desilylation and reduction as shown by Jacobsen⁶. Under nucleophilic aromatic substitution conditions, displacement of one of the chlorine substituents of 5- amino-4,6-dichloropyrimidine **17** by the amino group of **16** yielded the purine nucleoside precursor **18**. Heating **18** in diethoxymethyl acetate resulted in ring closure to give **19**. Ammonolysis of **19** led to **6**, while refluxing **19** in 1N hydrochloric acid yielded **8**.

Scheme 3 shows that compound **7** was accessible via standard carbocyclic ring construction⁷ using 2-amino-4,6-dichloropyrimidine **20** and amino alcohol **16**. Refluxing these starting materials in 1-butanol in the presence of triethylamine afforded **21**. Installation of the C-5 amino group on the pyrimidine ring began with a diazonium coupling reaction of **21** with 4-chlorobenzenediazonium chloride to yield **22**. The azo compound **22** was reduced with zinc and acetic acid and then cyclized using diethoxymethyl acetate to give **24**. The C-6 chlorine of **24** was replaced by an amino group in the final step.

Antiviral analysis

To investigate their biological potential, compounds **3–8** were subjected to antiviral screening versus hepatitis B virus. No activity was found. Furthermore, no cytotoxicity arose in the cell lines used in the antiviral assays.

Conclusion

The synthesis of several 2'- and 3'-deoxy derivatives of (+)-4'-deoxy-5'-noraristeromycin has been achieved. The use of amino alcohols such as **16** provides a convenient approach to enantiomerically pure modified nucleosides. The absence of antiviral activity suggests the importance of both 2' and 3' hydroxyl groups in the interaction with the biological target macromolecule.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported by funds from the Department of Health and Human Services (AI 083926). This support is greatly appreciated.

References

1. Koga M, Schneller SW. *Tetrahedron Lett.* 1990; 31:5861.
2. Seley KL, Schneller SW, Korba B. *Nucleosides and Nucleotides.* 1997; 16:2095.
3. Seley KL, Schneller SW, Korba. *J Med Chem.* 1998; 41:2168. [PubMed: 9622558]
4. Borcharding DR, Peet NP, Munson HR, Zhang H, Hoffman PF, Bowlin TL, Edwards CK. *J Med Chem.* 1996; 39:2615. [PubMed: 8691460]
5. Davol J. *J Chem. Soc.* 1960:131.
6. Martinez LE, Leighton IL, Carsten DH, Jacobsen EN. *J Am. Chem. Soc.* 1995; 117:5897.
7. Siddiqui SM, Jacobsen KA, Esker JL, Olah ME, Melman N, Tiwari KN, Secrist JA III, Schneller SW, Cristalli G, Stiles GL, Johnson CR, Ijzerman AP. *J. Med. Chem.* 1995; 38:1174. [PubMed: 7707320]

1. R=OH
2. R=H

- 3 X=N, R=H
4. X=N, R=NH₂
5. X=CH, R=H

- 6 R=H
7 R=NH₂

8

Figure 1.
Lead and target compounds

Scheme 1.
Preparation of 2^l-deoxy derivatives

a. 5-amino-4,6-dichloropyrimidine, 1-BuOH, Et₃N; b. (EtO)₂CHOAc, 90 °C;
c. NH₃/MeOH, 120 °C; d. 1N HCl

Scheme 2.
Preparation of 3'-deoxy derivatives

a. 1-BuOH, Et₃N; b. 4-benzenediazonium chloride, NaOAc, HOAc; c. zinc powder, HOAc, EtOH, H₂O; d. (EtO)₂CHOAc, 90 °C; e. NH₃/MeOH, 120 °C

Scheme 3.
Preparation of 7